Multiple Organ Dysfunction in a 33-Year-Old Woman Due to Hereditary Hemochromatosis

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MULTIPLE ORGAN DYSFUNCTION due to iron overload in patients with hereditary hemochromatosis is a preventable process, if the disorder is recognized early enough. Furthermore, some degree of organ dysfunction is often reversible with prompt implementation of appropriate treatment. Early diagnosis of this disease is crucial. Hemochromatosis symptomatically affects men in the fifth and sixth decades of life more often than women or younger men. The most frequent symptoms are weakness, lethargy, loss of libido, weight loss, and arthralgia. Later in the course of disease, it can lead to the development of diabetes mellitus or other organ failures such as that of liver or heart.[1] Although the signs and symptoms of hereditary hemochromatosis are usually less evident in menstruating women and younger men, it is important to be aware that this disease can affect both women and younger men as well.* Herein we present a case of hereditary hemochromatosis in a woman of childbearing age with substantial clinical manifestations, including new-onset diabetes, liver dysfunction, cardiac hypokinesis, and secondary hypogonadism.

Report of a Case

In October 1993, the patient, a 33-year-old woman with a 12-year history of amenorrhea, presented to the Emergency Department of Harbor-UCLA Medical Center with new-onset diabetes mellitus. She had progressively worsening nausea, vomiting, polyuria, polydipsia, malaise, and a 6.8-kg (15-lb) weight loss over three weeks. Her medical history included a left wrist fracture seven months before admission that was repaired by a bone graft from her right hip. The graft harvest site became infected, for which she received an eight-week course of antibiotics. She also had had meningitis as a teenager. She had two therapeutic abortions at ages 20 and 21. Shortly after the second abortion, the patient became amenorrheic. She had never had blood transfusions. She had smoked one pack of cigarettes per day for 15 years and drank alcohol occasionally but heavily at times. The family history was unremarkable for diabetes mellitus, cardiovascular disease, or hematologic disease.

On physical examination, the patient appeared anxious, was thin, and had a temperature of 37°C, a pulse rate of 77 beats per minute, blood pressure 99/66 mm of mercury, and respiratory rate 14 per minute. The skin over the entire body was noted to be light bronze. There was shotty, bilateral, anterior cervical lymphadenopathy. The lungs were clear to auscultation. The cardiac rhythm was regular, and the rate was normal. The abdomen was nontender, with a liver span of 10 cm.

Laboratory values were as follows: leukocyte count, 9.3×10^9 per liter (9,300 per mm^3); hemoglobin, 155 grams per liter (15.5 grams per dl); hematocrit, 0.44 volume fraction; platelet count, 102×10^9 per liter (102,000 per mm^3); serum sodium, 135, potassium, 4.9, chloride, 88, and bicarbonate, 19 mmol per liter; blood urea nitrogen, 3.4 mmol per liter (9 mg per dl); creatinine, 44.2 μmol per liter (0.5 mg per dl); glucose, 22.0 mmol per liter (397 mg per dl); serum acetone 3+; alanine aminotransferase, 93 U per liter; aspartate aminotransferase, 59 U per liter; alkaline phosphatase, 122 U per liter; albumin, 45 grams per liter (4.5 grams per dl); prothrombin time, 11.7 seconds; and partial thromboplastin time, 35.8 seconds.

An electrocardiogram showed sinus rhythm with multiple premature atrial complexes and nonspecific lateral T-wave changes. In addition, it showed low voltage in the frontal plane. A subsequent echocardiogram revealed a decreased left ventricular ejection fraction of 25%, with moderate mitral regurgitation. Radionuclide imaging confirmed the low ejection fraction.

A serum prolactin level was 9 μg per liter (9 ng per ml; normal, 0 to 25 ng per ml), a luteinizing hormone level was less than 3 IU per liter, the follicle-stimulating hormone level was less than 1.2 IU per liter, and total serum estrogen level was 41 ng per liter (normal, 61 to 394 ng per liter).

Finally, the iron studies showed an iron saturation of 92% with a serum iron level of 26.3 μmol per liter (147 μg per dl) and a total iron-binding capacity of 28 μmol per liter (159 μg per dl). The serum ferritin value was 4,290 μg per liter (4,290 ng per ml).

Based on the laboratory results, a liver biopsy was done that established the diagnosis of hemochromatosis. The biopsy specimen showed that the liver had a predominantly nodular pattern. Micronodules of liver were surrounded by fibrous tissue with focal bile duct metaplasia. The hepatocytes, Kupffer cells, and bile duct epithelial cells contained a granular golden pigment. These cells stained strongly positive with Prussian blue stain for iron (Figures 1, 2, and 3). HLA typing revealed the presence of the *A3* gene.

*See also the editorial by L. H. Smith Jr, MD, "Pumping Iron," on pages 370-372 of this issue.

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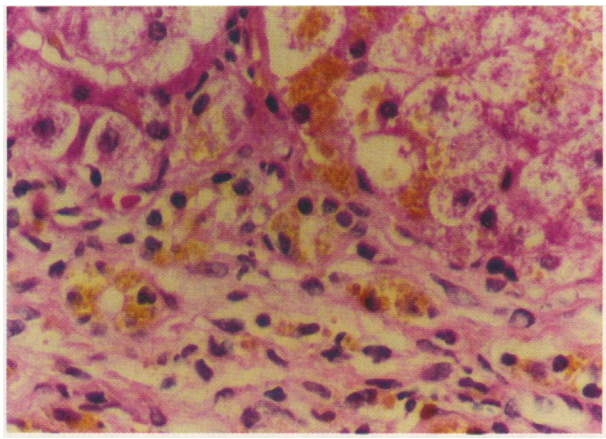

Figure 1.— A liver biopsy specimen shows hepatocytes filled with hemosiderin (light brown intracellular material [hematoxylin and eosin stain; original magnification, ×400]).

Discussion

Hereditary hemochromatosis is characterized by excessive absorption and accumulation of iron in various tissues. The early clinical manifestations include general symptoms such as weakness, lethargy, loss of libido, and weight loss. It also frequently causes arthralgia. The organs most frequently involved include the pancreas, liver, heart, endocrine organs, and skin.[1-3] A typical description of a patient with advanced disease is of a white man in the fifth to sixth decade of life with bronze-colored skin, diabetes, and testicular atrophy. The basic pathogenesis of iron accumulation is a genetic defect that results in increased iron absorption by the intestines.[3] These patients often carry the *HLA-A3* gene, which the patient in this report was found to carry.[4,5] Affected persons absorb about two to three times more iron per day than a normal person[2,3]—that is, about a 1- to 3-mg net gain of iron per day. When a cumulative iron load of 15 to 35 grams is reached, the person may become symptomatic.[2] Therefore, it usually takes 40 to 50 years before the disease may manifest itself clinically. In the case of a female patient, it is thought that iron loss due to menstruation and a relatively lower intake of iron delays or eliminates clinical manifestations of the disease.[2,6,7]

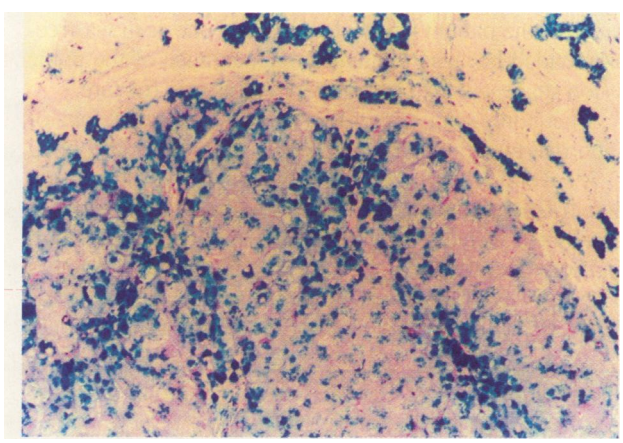

Figure 2.—Iron stain of the liver biopsy specimen shows substantial accumulation of iron in hepatocytes (Prussian blue stain; original magnification, ×100).

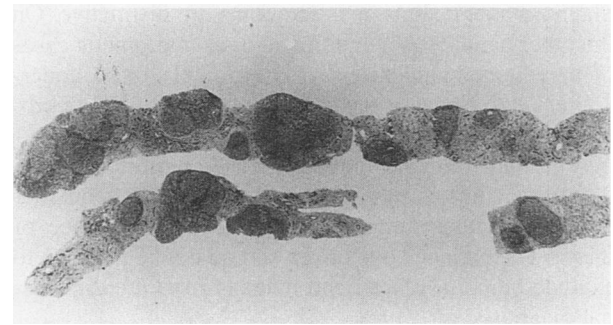

Figure 3.—Extensive micronodular cirrhosis consistent with severe hemochromatosis was noted in the liver biopsy specimen (hematoxylin and eosin stain; original magnification, ×20).

It is recognized that clinically symptomatic disease is seen in 1 in 200 people, but a heterozygous carrier for hemochromatosis may be found in 1 in 10 whites.[2,4] With a screening test of transferrin saturation, a value of 50% identifies nearly all persons who are homozygous for the disorder, regardless of sex or iron burden.[4] To make screening more specific, suggested threshold values for transferrin saturation during fasting are 60% for men and 50% for women.[4]

The case presented here is not unique from the standpoint of gene frequency, because white women have as high a gene frequency as white men. It is unique, however, for the age that clinical manifestations occurred and for their severity. The incidence of symptomatic hereditary hemochromatosis is much lower among women than men because of the factors mentioned earlier. In addition, even if the disease becomes clinically apparent, the age of onset is much later than that seen in our patient, usually in the fifth or sixth decade.[2,4] Our patient became amenorrheic at age 20. The cause of amenorrhea is likely secondary hypogonadism due to iron deposition in the anterior pituitary gland. The amenorrhea may be attributed to Asherman's syndrome brought on by a therapeutic abortion done just before the onset of her amenorrhea,[8] and it may be argued that the lack of menstruation and her history of alcohol intake exacerbated the rate of iron accumulation over the subsequent ten years. Even then, to have such substantial iron accumulation by age 33 is most unusual. In a search of the literature, only two other reports of symptomatic hereditary hemochromatosis with diabetes mellitus, secondary hypogonadism, and skin color change in young adult women were found.[9-11]

An advanced stage of hereditary hemochromatosis in a young woman is rare, but may not be difficult to

diagnose as the signs and symptoms are distinctive. On the other hand, less symptomatic or asymptomatic cases of hereditary hemochromatosis are likely to be underappreciated. Some of the early symptoms of hemochromatosis—weakness, lethargy, loss of libido, arthralgia—may be indistinguishable from those of more common disorders, and clinicians may need to consider hemochromatosis more frequently in the presence of these.[2] The patient's age or sex should not be a reason to exclude hereditary hemochromatosis from the differential diagnosis.

Screening for hemochromatosis is accomplished relatively easily. Some authors have advocated that the iron status of every patient be screened to evaluate for both iron overload and iron deficiency.[6] Although physicians may not consider measuring iron levels and total iron-binding capacity on every patient, they should keep in mind that hemochromatosis may be more prevalent than they think. It is important to prevent or reverse the complications of hemochromatosis with appropriate management during the early clinical stages.[12] It is especially important to note that women of childbearing age are not always protected from the clinical consequences of hereditary hemochromatosis, as exemplified by this case report.

We have described a common disorder with a rare presentation. Apparently no group is completely protected from this disease, including young women. Because the consequences of hereditary hemochromatosis are preventable or reversible to some degree with prompt treatment, early recognition of the disease is vital. Our case shows that a patient's being young or female should not be a reason to exclude hereditary hemochromatosis from the differential diagnosis when findings are suggestive of this disorder.

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Multiple Stress Fractures
An Unusual Presentation of Cushing's Disease

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STRESS FRACTURES occurring as a result of overzealous sports activities have become commonplace, but multiple stress fractures other than in a symmetric distribution are unusual. In the case reported here, the finding of multiple areas of abnormal uptake on a bone scan might have been mistaken for metastatic disease. Additional questioning of the patient and the often-requested "clinical correlation" led to the correct diagnosis of Cushing's disease. This case emphasizes the importance of the clinical history and the correlation of plain radiographs in interpreting skeletal scintigraphic findings.

Report of a Case

The patient, a 30-year-old woman, was seen initially with bilateral hip pain of one month's duration. The pain radiated to the groin and was aggravated on rising from a seated position. She had carried a diagnosis of schizoaffective disorder for the previous nine years. Her current medications were haloperidol, 10 mg at bedtime; trazodone hydrochloride, 300 mg at bedtime; and lorazepam, 0.5 mg twice a day.

An anteroposterior film of the pelvis showed an unusual crescentic lucency over the left pubis, resembling a "vacuum phenomenon" (Figure 1), and bilateral degenerative changes at the hips. Also noted was diffuse osteopenia. The rest of the pelvis was judged unremarkable, although visualization of the sacroiliac joints was suboptimal because of the patient's body habitus. A bone scan was recommended because the unusual appearance of the pubic lesion suggested the possibility of pathologic fracture.

The bone scan (Figure 2) showed multiple foci of abnormal tracer uptake consistent with fractures involving C-7, several ribs, the sacrum and sacroiliac joints, both iliac fossae, and the left superior and inferior pubic rami. Also noted were areas of increased activity along the medial proximal tibial diaphysis and in the metatarsal bones (Figure 3). On further questioning in the nuclear medicine department, the patient reported that for the past month

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